Preliminary communication

9-(β-D-Apio-L-furanosyl)-2-chloroadenine*

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(Received June 10th, 1969; in revised form July 10th, 1969)

The preparation of C-3'-modified purine nucleosides has both chemical and pharmacological interest in view of the recent syntheses of such compounds. These systems often exhibit antibiotic and/or antitumor activity. Some of these compounds are cordycepin (3'-deoxyadenosine)[1,2], puromycin[3], 3'-*C*-alkylerythrofuranosyl nucleosides[4,5] and, most recently, a nogalose (a 3'-*C*-methyl-D-allopyranose) nucleoside[6]. Our program on the chemistry of apiose[7] includes the production of nucleosides from this compound, which is one of the most widespread among naturally occurring branched-chain sugars.

We now wish to report the first synthesis of an apiosyl nucleoside of unequivocal structure.

The configuration at C-3 and C-5 of the D-apio-L-furanose system was locked by cyclocarbonation. Treatment of 1,2-*O*-isopropylidene-α-D-apio-L-furanose[8] (**1**) with *N,N'*-carbonyldiimidazole in tetrahydrofuran gave (92%) 3,5-*O*-carbonyl-1,2-*O*-isopropylidene-α-D-apio-L-furanose† (**2**), m.p. 113–114°; $[\alpha]_D^{22}$ + 63.7°, (*c* 1.9, chloroform); λ_{max}^{Nujol} 5.52 μm (–O–CO–O–). Sulfuric acid-catalyzed acetolysis of **2** in acetic acid–acetic anhydride yielded (42–59%) crystalline 1,2-di-*O*-acetyl-3,5-*O*-carbonyl-α and β-D-apio-L-furanose (**3**), m.p. 141.5–145°; $[\alpha]_D^{23}$ + 38.6° (*c* 1.1, chloroform); λ_{max}^{Nujol} 5.50 μm (–O–CO–O–) and 5.71 μm (OAc). The n.m.r. spectrum†† (chloroform-*d*) included: 6.44 (0.3-proton doublet, $J_{1,2}$ 4.5 Hz, H-1, 30% α-anomer) and 6.13 (0.7-proton singlet, H-1, 70% β-anomer). A syrupy product, partially characterized as 1,1,2,4-tetra-*O*-acetyl-3,5-*O*-carbonylapiose (**4**). (~40–49%) λ_{max} 5.52 μm (–O–CO–O–) and 5.71 μm (OAc); n.m.r. (chloroform-*d*): 6.96 (1-proton doublet, $J_{1,2}$ 3 Hz, H-1), was also formed during acetolysis of **2**.

Fusion of 2,6-dichloropurine (DCP) and **3** in the presence of dichloroacetic acid ($Cl_2CHCOOH$)[9] at 160° was successful. This technique, as found in other systems[10,11], gave a mixture (58%, after silica gel column chromatography) of α,β-anomers, 2,6-dichloro-9-(2'-*O*-acetyl-3', 5'-*O*-carbonyl-α-and β-D-apio-L-furanosyl)purine (**5a** and **5b**), m.p.

*Paper VI of a series of publications from this laboratory concerning the chemistry of apiose.

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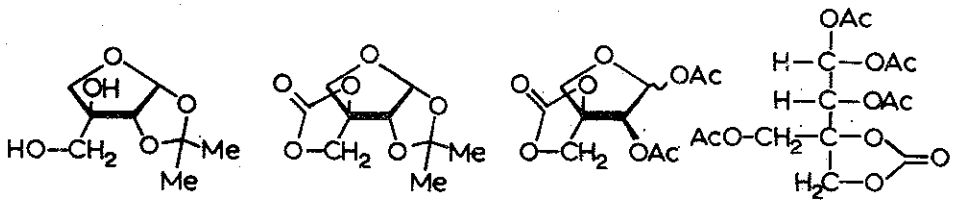
†Acceptable elemental analyses were obtained for all crystalline compounds reported. Melting points are uncorrected.

††100 MHz, with chemical shifts reported in δ units from a tetramethylsilane internal standard.



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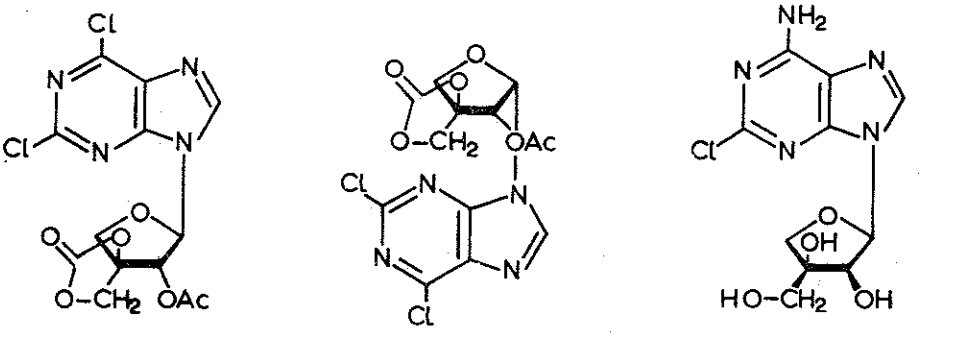

5a 5b 6

115–120°; n.m.r. (chloroform-*d*): 6.68 (0.32-proton doublet, $J_{1',2'}$ 5.5 Hz, H-1', 32% α-anomer)[12], and 6.26 (0.68-proton doublet, $J_{1',2'}$ 2.5 Hz, H-1', 68% β-anomer) [12]. The chromatographic mobilities of **5a** and **5b** were different but too similar to allow preparative-scale separation.

Condensation of DCP with **3** in nitromethane at reflux[13, 14], in the presence of dichloroacetic acid, gave only the pure branched-chain sugar nucleoside **5a** (51%, after silica gel column chromatography); m.p. 177–177.5°; $[\alpha]_D^{25}$ +55.0° (*c* 0.7, chloroform); λ_{max}^{Nujol} 5.49 (-O-CO-O-), 5.70 (OAc) and 6.25, 6.41 μm (C=N, C=C); λ_{max}^{EtOH} (pH 6) 255 shoulder (ε, 5660) and 274.5 nm (ε, 9650). Formation of **5a** in nitromethane, a solvent which promotes β-D anomer production in glycoside synthesis[15], was virtually stereospecific, as shown by the n.m.r. data (chloroform-*d*): 8.40 (1-proton singlet, H-8), 6.20 (1-proton doublet, $J_{1',2'}$ 2.5 Hz, H-1'), 5.67 (1-proton doublet, $J_{1',2'}$ 2.5 Hz, H-2'), 4.70, 4.18 (2-proton AB quartet, $J_{4',4'}$ 11 Hz, H-4'), 4.69, 4.40 (2-proton AB quartet, $J_{5',5'}$ 10 Hz, H-5'), and 2.22 (3-proton singlet, OAc). The β-D anomeric configuration was assigned to **5a** due to the observation of a narrow spacing (2.5 Hz) of the doublet[12] ascribable to H-1'. Predominant formation of a *trans* nucleoside would be expected from 2-*O*-acyl group participation[16].

Other Lewis acids, such as sulfamic acid[14] (76%) and boron trifluoride etherate (57%), also catalyzed the highly stereoselective formation of **5a**. Heating DCP with **3** in nitromethane for 1.5 day at 120° without catalyst, however, gave no product. It is known[17] that, in acidic media, DCP is hydrolyzed to xanthine. Under dry conditions,

during the synthesis of **5a** in the presence of dichloroacetic acid 27% of the DCP was converted into xanthine.

The convenient synthesis of **5a** opens the way to the production of various apiose nucleosides modified on the purine ring[18]. Ammonolysis of **5a** with saturated methanolic ammonia in a sealed tube[18,19], followed by picrate formation and liberation of the base with an aqueous suspension of AG 1–X4 (CO_3^{2-}) anion exchange resin gave the useful deblocked apioside (49%), 9-(β-D-apio-L-furanosyl)-2-chloroadenine (**6**), m.p. 137–138°; $[\alpha]_D^{26}$ - 16.0° (*c* 0.5, methanol); λ_{max}^{Nujol} 3.00, 3.20 (OH, NH), and 6.02, 6.27, 6.30 μm (NH, C=N, C=C); λ_{max}^{EtOH} (pH 6) 266 nm (ε, 15300); n.m.r. (deuterium oxide): 8.60 (1-proton singlet, H-8), 6.34 (1-proton doublet, $J_{1',2'}$ 2 Hz, H-1')[12], 4.90 (1-proton doublet, $J_{1',2'}$ 2 Hz, H-2'), 4.75 (2-proton singlet, H-5'), and 4.67, 4.63 (2-proton singlets, H-4').

Work on the synthesis of several derivatives of **5a** and **6** is in progress, and will be reported in full elsewhere.

ACKNOWLEDGMENT

The authors thank Mr. F. H. Bissett and Dr. R. C. Chalk for the measurement of n.m.r. spectra.

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